REMARKS

Claims 1-26 are pending after entry of this paper. Claims 1-22 have been rejected.

Claims 1, 10, 13, and 16 have been amended for clarification. Support may be found throughout the instant specification. Claim 10 has been amended for clarification. Support for the amendments may be found in paragraph 40 bridging pages 12 and 13 and paragraphs 61 and 62 on pages 21 and 22. No new matter has been introduced by these amendments. Reconsideration and withdrawal of the rejections are respectfully requested.

Claims 23-26 have been added and support may be found throughout the instant specification, for example at pages 93-96, and in the originally filed claims.

Information Disclosure Statement

Applicants acknowledge the consideration of the Information Disclosure Statement (IDS) submitted March 8, 2006.

Response to Rejections under 35 U.S.C. §112

Claims 1-9 and 13-15 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for lack of clarity as to whether the antibody binds to the first or the second of the two RNA:DNA hybrids, or to both, and for the role of the microarray bound biomolecule of step (b). Applicants respectfully disagree. However, for the sole purpose of advancing the instant application, applicants have amended the claims in order to address the Examiner's concerns. Reconsideration and withdrawal of the §112 rejection are respectfully requested.

With respect to claims 13-15, the Examiner's attention is respectfully directed to the assay shown in Figure 5D, which describes using the signal from the hybridized detectably-labeled complementary nucleic acid probe of step (b) to normalize the signal resulting from detection of the RNA:DNA hybrid of step (a). The claim should also be amended as follows to help clarify the meaning of the claims. For the sole purpose of advancing the instant application, applicants have amended the claims in order to address the Examiner's concerns. Reconsideration and withdrawal of the §112 rejection are respectfully requested.

Response to Rejections under 35 U.S.C. §102

Claim 10 has been rejected under 35 U.S.C. §102(b) as being anticipated by Coutlee, et al. (Anal. Biochem., 181:153-162, 1989). Applicants respectfully disagree.

Coutlee describes a hybridization reaction performed in solution with subsequent capture of labeled probe-target hybrids on a microtiter plate. As described in the schematic diagram of Figure 1, the RNA target hybridizes with the biotinylated DNA probe, and then the RNA:DNA hybrid binds to the immobilized anti-biotin surface (see, pg. 156). Furthermore, under "Results" on page 156 of Coutlee, the "[b]iotin-labeled DNA-RNA hybrids are then bound in an immunoreaction to the wells of a microtiter plate coated with a polyclonal antibiotin antibody". Applicants point out that not only is the Coutlee method different, but also uses a microtiter plate, while the instant invention is directed to a microarray method.

Microarrays comprise an orderly arrangement of a plurality of samples or biological molecules in a very small area, as described in the instant specification on page 18, par. 56 through page 21, par. 59. Coutlee does not teach or suggest the very specific application of the biological molecules on microarrays. Applicants respectfully direct the Examiner's attention to Coutlee, page 16, lines 12-14 which describes using microtiter plates and nitrocellulose filters, but does not even contemplate using microarrays having an ordered array of biological molecules. Applicants assert that the microarray method utilizes methods where all of the biological molecules that are immobilized undergo the same treatment. The microarray method of the instant invention utilizes a single solid support for a plurality of biological molecules. Whereas, the microtiter plate wells provide separate environments, and do not undergo the same treatment. Thus, these methods are technically different, and microarray methods are novel and inventive over such a microtiter method. Therefore, because the method steps in claim 10 as presented herein are different from the method disclosed in Coutlee, and because the Coutlee method does not use a microarray, the instant invention of claim 10 is novel over Coutlee. Reconsideration and withdrawal of the instant §102 rejection are respectfully requested.

Response to Rejections under 35 U.S.C. §103

Claims 10-12 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Coutlee, et al. The Examiner admits that Coutlee does not show repetition of the assay, either sequentially or simultaneously (Office Action- page 5), and further contends that it would have been obvious for the skilled artisan to "modify the method of Coutlee et al. by repeating the assay either sequentially or simultaneously because Coutlee et al. shows analysis of multiple samples and repetition of assays must be done either simultaneously or sequentially" (Office Action- page 5). Applicants respectfully disagree.

Regardless of whether or not one skilled in the art would have modified the method of Coutlee to repeat the assay, the method described in Coutlee teaches solution hybridization, *i.e.*, prior to binding the hybrid to a solid support, not forming an immobilized hybrid as claimed. As previously mentioned, Coutlee does not describe a microarray method. Therefore, because Coutlee does not teach or suggest a microarray hybridization method, where hybridization occurs on a solid support, nor provide guidance for repeating the assay in a sequential or simultaneous manner, Coutlee does not make obvious the claimed invention. Reconsideration and withdrawal of the §103 rejection is respectfully requested.

Claims 16-22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Carrico (U.S. Patent No. 5,200,313) in view of Lockhart, et al. (Nature Biotech., 14:1675-1680, 1996) in view of WO 93/10263 (the "WO '263 publication") to Digene Diagnostics. The Examiner contends that it would have been obvious to a skilled artisan to modify the method of Carrico with the high density array of short probes of Lockhart, and to treat the hybridized samples with RNase to facilitate removal of unhybridized probe as described by the WO '263 publication. Applicants respectfully disagree with the Examiner's contention.

Carrico describes a hybridization method where the target or sample nucleic acid hybridizes with an immobilized or immobilizeable nucleic acid probe (col. 7, lns. 10-20). As acknowledged by the Examiner, Carrico also does not use microarrays.

The method described in Carrico requires "a single probe element" (col. 2, lns. 64-67; emphasis added). Figures 1 and 2 of Carrico show one sample nucleic acid and one probe forming a hybrid. In particular, Carrico describes the formation of a complex of two moieties or

molecules, specifically two nucleic acids. Carrico does not teach or suggest the use of a complex of more than two nucleic acid molecules.

The Examiner combines Lockhart for showing DNA arrays and methods of using such arrays. Neither Carrico nor Lockhart teach or suggest the use of a second nucleic acid as part of a tripartite hybrid as presently claimed in the instant application. The Examiner further combines the WO 93/10263 publication with Carrico and Lockhart to reject claims using RNase (*i.e.*, claims 16-22). However, the WO '263 publication does not remedy the deficiencies of Carrico and Lockhart. Therefore, the combination of Carrico, Lockhart, and the WO '263 publication does not make obvious the instantly claimed invention of a kit for detecting RNA:DNA hybrids with a microarray solid support that has nucleic acids immobilized thereto which are complementary to target nucleic acids, a hybridization buffer, a wash buffer, an RNase, an antibody specifically reactive with an RNA:DNA hybrid, and a biomolecule probe that hybridizes to a portion of the immobilized nucleic acid or target nucleic acid. Reconsideration and withdrawal of the §103 rejection is respectfully requested for the above reasons.

CONCLUSION

Based on the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 2629-4036.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 2629-4036.

Respectfully submitted,
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